IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Application No. 10/806,088

Applicant: Flack et al.

Filed: March 22, 2007

TC/AU: 1614

Examiner: James D. Anderson

Docket No.: 225011 (Client Reference No. E-133-1990/0-US-03)

Customer No.: 45733

APPELLANTS' APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In support of the appeal from the final rejection dated March 19, 2007, Appellants now submit their Brief.

Real Party In Interest

The patent application that is the subject of this appeal is assigned to the Government of the United States of America, represented by the Secretary, Department of Health and Human Services. The patent application has been licensed to Ascenta Therapeutics, Inc.

Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal.

Status of Claims

Claims 8-14, 16, and 38-43 are currently pending and are the subject of this appeal. Claims 1-7, 15, and 17-37 were canceled in the "Reply to Office Action" dated October 20, 2006. The pending claims are reproduced in the "Claims Appendix" attached hereto.

Status of Amendments

No amendments were made in response to the final rejection set forth in the Office Action dated March 19, 2007.

Summary of Claimed Subject Matter

Claim 8 is the only independent claim currently pending. Independent claim 8 is directed to a method for treating a cancer in a human wherein the cancer is susceptible to treatment with gossypol, a physiologically acceptable salt of gossypol, or a combination thereof. The method comprises administering to the human a composition comprising an anti-cancer effective amount of at least one compound selected from the group consisting of gossypol and a physiologically acceptable salt thereof (as supported at column 2, lines 60-65, and column 3, lines 6-11), wherein the gossypol compound is administered with a pharmaceutically acceptable carrier (supported at column 7, lines 24-29) and wherein the gossypol compound exhibits an overall effect of rotating the plane of polarized light in the (-)- direction (supported at column 7, lines 62-66).

The method described in claim 8 is dependently claimed for the treatment of adrenal (claims 9 and 10 as supported at column 2, lines 20-25), ovarian (claims 9 and 38 as supported at column 2, lines 20-25), thyroid (claims 9 and 39 as supported at column 2, lines 20-25), testicular (claims 9 and 40 as supported at column 2, lines 20-25), pituitary (claims 9 and 41 as supported at column 2, lines 20-25), prostate (claims 9 and 42 as supported at column 1, lines 46-62), and breast cancers (claims 9 and 43 as supported at column 1, lines 12-16, and column 1, lines 46-62). The method described in claim 8 is also dependently claimed for the treatment of cancer that is a carcinoid tumor of neuroendocrine tissue located in the lung, pancreas, or gastrointestinal tract (claim 16 as supported at column 2, lines 20-25).

With respect to the method described in claim 8, a dependent claim wherein the blood concentration of the compound is 200-1000 ng/dl (claim 11 as supported at column 7, Table 4), is also provided.

In the method described in claim 8, dependent claims wherein the compound can be administered parenterally at a dose of 1-2 mg/d (claim 12 as supported at column 7, Table 4),

orally at a dose of 20-100 mg/d (claim 13 as supported at column 7, Table 4), or rectally at a dose of 40-140 mg/d (claim 14 as supported at column 7, Table 4), are also provided.

Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 8-10, 16, and 38-43 are unpatentable under 35 U.S.C. § 103(a) over Wu (*Cancer Research*, 49: 3754-3758 (1989)) in view of Band (*Gynecologic Oncologists*, 23: 261 (1986)), Zhang (*Acta Academiae Medicinae Sinicae*, 7: 384-387 (1985)), and other relevant prior art.

2. Whether claims 11-14 are unpatentable under 35 U.S.C. § 103(a) over Wu (1989), Band (1986), and Zhang in further view of Wu (*Clin. Pharmacol. Ther.* 39: 613-618 (1986)) and other relevant prior art.

Argument

The Examiner maintains that (1) the invention defined by claims 8-10, 16, and 38-43 is obvious over the disclosures of Wu (1989), Band (1986), and Zhang and (2) the invention defined by claims 11-14 is obvious over the disclosures of Wu (1989), Band (1986), Zhang, and Wu (1986).

These two obviousness rejections are separately discussed below. The patent law concerning obviousness is applicable to both rejections.

A patent claim is invalid if, at the time the invention was made, the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (a) the scope and content of the prior art, (b) the level of ordinary skill in the prior art, (c) the differences between the claimed invention and the prior art, and (d) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467. In opining on the proper application of *Graham*, the Supreme Court has explained that, as illustrated in *United States* v. *Adams*, 383 U.S. 39, 148 U.S.P.Q. 479 (1966), "when the prior art teaches away from

combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious" *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740, 82 U.S.P.Q.2d 1385, 1395 (2007).

Appellants submit that the Examiner has erred in determining the scope and content of the prior art and by not considering prior art which taught away from the practice of the invention. In addition, the Examiner has erred in determining that the invention was *prima facie* obvious.

1. Rejection of Claims 8-10, 16, and 38-43 Over Wu (1989), Band (1986), and Zhang

The subject matter of claims 8-10, 16, and 38-43 is unobvious over a properly determined scope of the prior art, as is apparent from a discussion of the four *Graham* factors.

a. The Scope and Content of the Prior Art

Band (1986) discloses the *in vitro* testing of gossypol optical isomers on just cancer cell lines; specifically cell lines of ovarian and testicular cancer as well as of mesodermal tumor of uterine origin. In this context Band (1986) discloses that (-)-gossypol is more potent than (+)-gossypol at killing the cancer cells and speculates that it may be clinically useful in the treatment of reproductive tract cancers.

Band, Gynecologic Oncology 32:273-277 (1989), is a subsequent publication by the same investigators. Band (1989) describes studies where the activity of the gossypol enantiomers was compared in both cancerous and normal cell lines. In Table 1 on page 276, Band (1989) presents data showing the non-selective activity of (-)-gossypol. In this subsequent and more clinically relevant study, the same investigators concluded that the anti-proliferative action of gossypol is non-selective with respect to cell type, thereby making it lethal to normal, non-cancerous, reproductive tract cells as well as cancer cells. The Examiner failed to consider the teachings of Band (1989) when determining the scope and content of the prior art and the obviousness of the claimed invention.

Wu (1989) discloses the use of racemic gossypol on cell lines *in vitro* and *in vivo* in mice. Wu (1986) discloses that racemic gossypol has antispermatogenic activity and examines the pharmacokinetics of gossypol in humans and dogs. However, there is no

teaching or suggestion in Wu (1989) or Wu (1986) that gossypol is effective to treat cancer in humans.

Zhang discloses that (-)-gossypol is more effective than (+)-gossypol and racemic gossypol in the treatment of HeLa cells *in vitro*. There is no teaching in Zhang that (-)-gossypol is effective to treat cancer in humans.

b. Level of Ordinary Skill in the Art

While no findings were made during prosecution concerning the level of ordinary skill in the art, the level of ordinary skill in the art can be considered to be relatively high, such that one of ordinary skill in the art can be considered to be a person with a doctorate or medical degree and several years of experience in the field of cancer treatment.

c. Differences Between Claimed Invention and Prior Art

The present invention as defined by the rejected claims is a method for treating a cancer in a human by administration of an anti-cancer effective amount of (-)-gossypol (see sole independent claim 8). The cancer can be, *inter alia*, adrenal, ovarian, thyroid, testicular, pituitary, prostate, or breast cancer, or a carcinoid tumor of neuroendocrine tissue located in the lung, pancreas, or gastrointestinal tract (which cancers are recited in dependent claims 9-10, 16, and 38-43).

None of the cited references discloses the use of (-)-gossypol to treat a cancer of any type in humans. Moreover, the disclosures of the cited references – especially in the context of the scope and content of the relevant prior art as of the effective filing date for the present application – do not reasonably convey to one of ordinary skill in the art that (-)-gossypol would or could be effective in the treatment of a cancer of any type in humans. In fact, the relevant prior art teaches away from the invention.

The fact that one of ordinary skill in the art, considering the prior art, would not have thought that (-)-gossypol could be used to effectively treat cancer in a human results, at least in part, from the a report on the lack of specificity of (-)-gossypol in inducing cell death. In particular, Band (1989) reported on the effect of the individual gossypol enantiomers on both cancerous and normal cell lines and concluded that the anti-proliferative action of gossypol and each of its enantiomers is non-selective, thereby making it lethal to normal,

non-cancerous, reproductive tract cells as well as the intended cancer cell targets. This teaches away from the treatment of cancer with (-)-gossypol as one of ordinary skill in the art would believe, based upon Band (1989), that (-)-gossypol would have significant side effects which would prevent the use of doses that are high enough be useful for treatment of cancer.

Thus, the relevant prior art would not have led one of ordinary skill in the art to reasonably expect that (-)-gossypol would be an effective treatment of cancer in humans, particularly in view of the teachings of the non-selective cytotoxicity of gossypol in Band (1989).

Further, although the Examiner asserted that (+)-gossypol is the likely cause of gossypol toxicity (thereby suggesting that one of ordinary skill in the art would be directed to use (-)-gossypol), Wu (1986) points out that, albeit in the primary context of testing for antispermatogenetic effect, "only (-)-gossypol exhibited both efficacy and toxicity *in vivo*, whereas (+)-gossypol was inactive and of low toxicity." As stated by the Examiner in the final Office Action, "*in vitro* and *in vivo* testing are established models for evaluating anticancer activity" (Office Action dated March 19, 2007, p. 4). Therefore, in view of the *in vitro* toxicity of gossypol to both cancerous and noncancerous human cells as reported by Band (1989), one of ordinary skill in the art would not have reasonably concluded that gossypol would not be toxic to noncancerous human cells *in vivo* while still having the desired activity with respect to cancerous cells. In addition, based on the more thorough and well controlled teachings of Band (1989), one of ordinary skill would not have been motivated to try (-)-gossypol in the treatment of human cancer, let alone reasonably expect that it would be safe and effective to treat cancer in a human.

As of the effective filing date for the present application, one of ordinary skill in the art would not have believed that it would have been possible to successfully determine a safe and effective dosage range in genetically heterogenous humans for a drug that displays such a general toxic effect *in vitro* and such a narrow window of efficacy and safety in a genetically homogenous population of in-bred rodents (see Declaration of Dr. Marcus Reidenberg, dated May 27, 1998, and submitted with the "Reply to Office Action" dated May 12, 2005). Therefore concluding that (-)-gossypol would be readily predicted to have the appropriate efficacy profile to treat cancer in a human based on the teachings in the prior art at the time of filing is not justified.

d. Objective Evidence of Non-Obviousness

(-)-Gossypol has proven clinically effective in the treatment of several types of cancer in humans (see Declaration of Dr. Jon T. Holmlund, dated August 24, 2006, and submitted with the "Reply to Office Action" dated October 20, 2006). To turn a phrase from the U.S. Supreme Court's recent *KSR* decision, the combination of elements that comprise the claimed invention did *not* yield the predicted results. In view of the experimental data reported in the prior art tending to show that (-)-gossypol would not be effective in the treatment of cancer in humans, the fact that (-)-gossypol has proven effective in the treatment of cancer in humans is surprising and further evidences the unobviousness of the claimed invention.

2. Rejection of Claims 11-14 Over Wu (1989), Band (1986) Zhang, and Wu (1986)

The subject matter of claims 11-14 is unobvious over the combined disclosures of Wu (1989), Band (1986), Zhang, and Wu (1986) as is apparent from a discussion of the four *Graham* factors.

a. The Scope and Content of the Prior Art

The cited references for the obviousness rejection of claims 11-14 are the same as the cited references for the obviousness rejection of claims 8-10, 16, and 38-43, except for the Examiner's additional reliance on Wu (1986).

Wu (1986) discloses that gossypol has antispermatogenic activity and examines the pharmacokinetics of gossypol in humans and dogs. However, there is no teaching in Wu (1986) that gossypol is effective to treat cancer in humans.

Band (1989) presents data showing the non-selective activity of (-)-gossypol and concludes that the anti-proliferative action of gossypol is non-selective with respect to cell type, thereby making it lethal to normal, non-cancerous, reproductive tract cells as well as cancer cells. The Examiner failed to consider the teachings of Band (1989) when determining the scope and content of the prior art and the obviousness of the claimed invention.

b. Level of Ordinary Skill in the Art

As indicated in connection with the discussion of the other obviousness rejection above, while no findings were made during prosecution concerning the level of ordinary skill in the art, the level of ordinary skill in the art can be considered to be relatively high such that one of ordinary skill in the art can be considered to be a person having a doctorate or medical degree and several years of experience in the field of cancer treatment.

c. Differences Between Claimed Invention and Prior Art

The present invention as defined by the rejected claims is a method for treating a cancer in a human by administration of an anti-cancer effective amount of (-)-gossypol, wherein the blood concentration of the (-)-gossypol is 200-1000 ng/dl (claim 11), the (-)-gossypol is administered parenterally at a dose of 1-2 mg/d (claim 12), the (-)-gossypol is administered orally at a dose of 20-100 mg/d (claim 13), or the (-)-gossypol is administered rectally at a dose of 40-140 mg/d (claim 14).

None of the cited references discloses the use of (-)-gossypol to treat a cancer of any type in humans, let alone using administration routes and amounts of (-)-gossypol recited in any of rejected claims 11-14. Moreover, the disclosures of the cited references – especially in the context of the prior art as of the effective filing date for the present application – do not reasonably convey to one of ordinary skill in the art that (-)-gossypol would or could be effective in the treatment of a cancer of any type in humans, particularly using the administration routes and amounts of (-)-gossypol recited in any of rejected claims 11-14.

The discussion above in connection with the other obviousness rejection as to the differences between the present invention as defined by claims 8-10, 16, and 38-43 and the prior art is equally applicable here with respect to the present invention as defined by rejected claims 11-14. The additional cited reference of Wu (1986) with respect to this obviousness rejection as compared to the other obviousness rejection is of no consequence inasmuch as Wu (1986) does not satisfy the deficiencies of the other cited references as discussed above. In addition, since each of claims 11-14 specifies a particular administration route and/or dose of (-)-gossypol (which features are not recited in the claims subject to the other obviousness rejection), and since the cited references do not disclose the additional features recited in claims 11-14, the present invention as defined by rejected claims 11-14 is even further

removed from the prior art as compared to the present invention as defined by claims 8-10, 16, and 38-43.

As discussed in more detail with respect to the other obviousness rejection, the fact that one of ordinary skill in the art, considering the entire scope of the relevant prior art, would not have thought that (-)-gossypol could be used to effectively treat cancer in a human results, at least in part, from the lack of specificity of (-)-gossypol as reported in Band (1989). In view of the *in vitro* toxicity of gossypol to both cancerous and noncancerous human cells as reported by Band (1989), one of ordinary skill in the art would not only have reasonably concluded that gossypol would be toxic to cancerous and noncancerous human cells *in vivo*, but also would not have been motivated to try (-)-gossypol in the treatment of human cancer. In fact, the relevant prior art teaches away from the claimed invention. Furthermore one would not reasonably expect that it would be safe and effective to treat cancer in a human by being administered in the specified manners and in the defined doses recited in rejected claims 11-14.

As of the effective filing date for the present application, one of ordinary skill in the art would not have believed that it would have been possible to successfully determine a safe and effective dosage range in genetically heterogenous humans for a drug that displays such a general toxic effect *in vitro* and such a narrow window of efficacy and safety in a genetically homogenous population of in-bred rodents (see Declaration of Dr. Marcus Reidenberg, dated May 27, 1998, and submitted with the "Reply to Office Action" dated May 12, 2005). The efficacy of (-)-gossypol to treat cancer in a human would not have been considered predictable based on the teachings in the prior art.

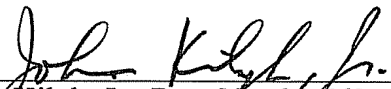
d. Objective Evidence of Non-Obviousness

(-)-Gossypol has proven effective in the treatment of cancer in humans (see Declaration of Dr. Jon T. Holmlund, dated August 24, 2006, and submitted with the "Reply to Office Action" dated October 20, 2006). In view of the experimental data reported in the prior art tending to show that (-)-gossypol would not be effective in the treatment of cancer in humans, the fact that (-)-gossypol has proven effective in the treatment of cancer in humans is surprising and further evidences the unobviousness of the claimed invention as defined by rejected claims 11-14.

Conclusion

For the foregoing reasons, Appellants respectfully request the reversal of the rejections of the subject patent application.

Respectfully submitted,



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Claims Appendix

1. (Canceled) [A method for treating a cancer in a human, wherein the cancer is susceptible to treatment with gossypol, a physiologically acceptable salt of gossypol, gossypolone, a physiologically acceptable salt of gossypolone, or any combination thereof, which method comprises:

administering to said human an anti-cancer effective amount of at least one compound selected from the group consisting of gossypol, a physiologically acceptable salt of gossypol, gossypolone, and a physiologically acceptable salt of gossypolone, and a pharmaceutically acceptable carrier.]

2. (Canceled) [The method of claim 1, wherein said cancer is adrenal, ovarian, thyroid, testicular, pituitary, prostate, or breast cancer.]

3. (Canceled) [The method of claim 2, wherein said cancer is adrenal cancer.]

4. (Canceled) [The method of claim 1, wherein the blood concentration of said compound is 400-1000 ng/dl.]

5. (Canceled) [The method of claim 4, wherein said compound is gossypolone or a physiologically acceptable salt of gossypolone.]

6. (Canceled) [The method of claim 5, wherein said gossypolone or physiologically acceptable salt of gossypolone is administered orally, rectally or vaginally at a dose of 50-200 mg/d.]

7. (Canceled) [The method of claim 5, wherein said gossypolone or physiologically acceptable salt of gossypolone is administered parenterally at a dose of 1-5 mg/kg/d.]

8. (Pending – Fourth Amendment) A method for treating a cancer in a human, wherein the cancer is susceptible to treatment with gossypol, a [pharmaceutically] <u>physiologically</u> acceptable salt of gossypol, or a combination thereof, which method comprises:

administering to said human a composition comprising an anti-cancer effective amount of at least one compound selected from the group consisting of gossypol and a physiologically acceptable salt thereof, [and] wherein the at least one compound is administered with a pharmaceutically acceptable carrier, and wherein the at least one compound exhibits an overall effect of rotating the plane of polarized light in the (-) direction.

9. (Pending - Never Amended) The method of claim 8, wherein said cancer is adrenal, ovarian, thyroid, testicular, pituitary, prostate, or breast cancer.

10. (Pending – Never Amended) The method of claim 8, wherein said cancer is adrenal cancer.

11. (Pending – Twice Amended) The method of claim 8, wherein the blood concentration of said compound is [400] 200-1000 ng/dl.

12. (Pending – Once Amended) The method of claim 8, wherein said compound is administered parenterally at a dose of 1-2 mg/d.

13. (Pending – Once Amended) The method of claim 8, wherein said compound is administered orally at a dose of 20-100 mg/d.

14. (Pending – Once Amended) The method of claim 8, wherein said compound is administered rectally at a dose of 40-140 mg/d.

15. (Canceled)

16. (Pending – Never Amended) The method of claim 8, wherein said cancer is a carcinoid tumor of neuroendocrine tissue located in the lung, pancreas, or gastrointestinal tract.

17.-37. (Canceled)

38. (Pending – New) The method of claim 8, wherein said cancer is ovarian cancer.

39. (Pending – New) The method of claim 8, wherein said cancer is thyroid cancer.

40. (Pending – New) The method of claim 8, wherein said cancer is testicular cancer.

41. (Pending – New) The method of claim 8, wherein said cancer is pituitary cancer.

42. (Pending – New) The method of claim 8, wherein said cancer is prostate cancer.

43. (Pending – New) The method of claim 8, wherein said cancer is breast cancer.

Evidence Appendix

1. Band, *Gynecologic Oncology*, 32: 273-277 (1989), entered into evidence by way of the Information Disclosure Statement dated March 22, 2004.
2. Declaration of Dr. Marcus Reidenberg, dated May 27, 1998 and entered into evidence by way of the "Reply to Office Action" dated May 12, 2005.
3. Declaration of Dr. Jon T. Holmlund, dated August 24, 2006, and entered into evidence by way of the "Reply to Office Action" dated October 20, 2006.

Related Proceedings Appendix

Not Applicable